



Exploring the role of competition induced by non-vaccine serotypes for herd protection following pneumococcal vaccination

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Title: Exploring the role of competition induced by non-vaccine serotypes for herd protection following pneumococcal vaccination

Running head: Competition and pneumococcal vaccination

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13 **Abstract**

14 The competitive pressure from non-vaccine serotypes may have helped pneumococcal conjugate vaccines
15 (PCVs) to limit vaccine serotype (VT) prevalence. We aim to investigate if, consequently, the indirect protection
16 of higher valency vaccines could fall short of the profound effects of current formulations.

17 We compare three previously described pneumococcal models harmonized to simulate 20 serotypes with a
18 combined pre-vaccination prevalence in <5y old children of 40%. We simulate vaccines of increasing valency by
19 adding serotypes in order of their competitiveness and explore their ability to reduce VT carriage by 95% within
20 10 years after introduction.

21 All models predict that additional valency will reduce indirect vaccine effects and hence the overall vaccine
22 impact on carriage both in children and adults. Consequently, the minimal effective coverage (efficacy against
23 carriage * vaccine coverage) needed to eliminate vaccine type carriage increases with increasing valency. One
24 model predicts this effect to be modest while the other two predict that high-valency vaccines may struggle to
25 eliminate VT pneumococci unless vaccine efficacy against carriage can be substantially improved. Similar
26 results were obtained when settings of higher transmission intensity and different PCV formulations were
27 explored.

28 Failure to eliminate carriage as a result of increased valency could lead to overall decreased impact of
29 vaccination if the disease burden caused by the added serotypes is low. Hence a comparison of vaccine
30 formulations of varying valency, and pan-valent formulations in particular, should consider the invasiveness of
31 targeted serotypes, as well as efficacy against carriage.

Background

In 2000 the first pneumococcal conjugate vaccine (PCV), which provided protection against seven of the most pathogenic pneumococcal capsular serotypes, was licensed and recommended for immunization of infants in the US [1]. Subsequently, 10- and 13-valent formulations have been licensed and are now being used to prevent pneumococcal disease in more than 130 countries worldwide [2–11]. The incidence of carriage and disease associated with vaccine type serotypes (VT) declined in vaccinated children, and also in unvaccinated children and adults, after PCVs were introduced into national immunization programmes [12]. However, the overall prevalence of pneumococcal carriage remained approximately constant as non-vaccine serotypes (NVT), i.e., serotypes not targeted by the vaccine, filled the ecological niche [13]. The increased disease from these serotypes has partially offset the benefit of pneumococcal vaccination. As a result pneumococcal vaccines that target more or all serotypes are being developed [14].

Previous work has suggested that the competition between vaccine type (VT) and non-vaccine type (NVT) serotypes plays an important role in the herd protection observed in the post PCV era [15–17]. In particular, by reducing acquisition of VT carriage, pneumococcal conjugate vaccines give NVTs a competitive advantage over VTs in the nasopharynx. Thus, in vaccinated populations the presence of NVT in vaccinated hosts provides additional competitive pressure, which combines with the immune protection afforded by the vaccine, to suppress VT colonization. Moreover, at the population level, there is competition between VT and NVT in non-vaccinated hosts, and the spread of VT is likely inhibited by competition from NVT in non-vaccinated people as well. In each of these cases, the mechanisms of competition might include direct competition in the nasopharynx [18], induction of innate immune effectors by NVT that also inhibit VT [19], and induction of forms of acquired immunity that also inhibit VT, such as Th17-based and antibody-based immunity to conserved antigens [20–22]. For higher valent pneumococcal vaccines, including those that target proteins common to most pneumococci [14], this hypothesis implies that, by effectively losing the benefit of NVT competition, even with similar vaccine efficacy against pneumococcal carriage and disease, levels of indirect protection in unvaccinated individuals could fall short of the profound effects that have been observed with the routine use of conjugate vaccines.

In this paper we explored three previously developed dynamic modelling approaches for pneumococcal ecology as to whether they predict a similar qualitative contribution of NVT competition to the indirect effects of pneumococcal vaccination. We harmonized key model parameters that govern vaccine efficacy and pneumococcal epidemiology in the absence of vaccination and explored various vaccine scenarios to better understand the role of competition in providing protection.

Methods

Models

The model by Bottomley et al [16] (M_B) is a deterministic model that represents the pre-PCV steady state of pneumococcal infections in the Gambia and was used to predict the impact of introduction of PCV13 into the childhood vaccination program. It is fitted to local longitudinal pre-vaccination carriage data. Serotypes are grouped into three classes of transmissibility (low, medium, high) and clearance rate (high, medium, low).

Serotypes within the same group share the same properties. Pneumococcal carriers are assumed to gain partial immunity against acquisition of new serotypes during the episode of carriage, which represents the mechanism of serotype competition, and a proportion of clearances leads to life-long immunity against the cleared serotype, which balances competitive advantages to sustain serotype diversity. The default model parameterization is the same as reported in the original manuscript.

The model by Cobey & Lipsitch [23] (M_CL) is an individual-based model that represents a generic high-income setting. Serotypes differed by their intrinsic duration of carriage and their in vivo competitive ability. Pneumococcal carriers are assumed to gain partial protection, quantified by the competitive ability of the resident type, against acquisition of additional serotypes during the episode of carriage, which represents the mechanism of competition. Following clearance, the host's susceptibility to any subsequent homologous acquisition as well as the duration of any subsequent carriage episode is reduced. The strength of acquired immunity that reduces carriage duration was fitted to observations from a longitudinal carriage study in infants[24]. Acquired The serotype-specific immunity accentuates within-serotype competition thus providing balancing selection on serotypes, and acquired immunity independent of capsule reduces fitness differences. The simulations presented in this work rely on the default model parameterization, i.e. homogeneous mixing, the default rate of acquisition of capsular immunity ($\sigma = 0.3$) and the default rate of acquisition of nonspecific immunity assuming non-linear reduction in carriage duration ($\epsilon = 0.25$).

The model by Flasche et al [15] (M_F) is an individual based model that generalizes the most commonly used deterministic pneumococcal model [17,25,26]. It represents a generic high income country setting. Serotypes differ by their intrinsic duration of carriage. Duration of carriage and susceptibility to acquisition decline with age but are exposure independent. The acquisition of a pneumococcus triggers both a transient homologous immune response, which represents serotype competition, and a transient heterologous immune response, which represents the mechanism to ensure serotype coexistence. Both immune responses are assumed to prevent additional acquisition of respective serotypes. Unless mentioned otherwise the simulations presented in this work rely on the default model parameterization, i.e. the duration of specific and non-specific immunity was 9 and 18 weeks respectively.

While there was no formal model selection process we included models that span most of the range of alternative dynamic pneumococcal model assumptions on serotype competition and natural immunity (ie M_F includes most deterministic modelling approaches to date). An overview of the different modelling approaches in this study is shown in Table 1. The main differences between models in regards to this work are the assumptions on acquired immunity and the resulting mechanisms for competition and serotype coexistence.

Analyses

We harmonized models to simulate 20 artificial serotypes with a combined pre-vaccination prevalence in <5y old children of 40%, approximating a high income setting with moderate transmission, or 70%, approximating a low income setting with high transmission intensity. In M_B serotypes were evenly distributed between the three classes, i.e. 7, 7,6 serotypes of low, mid and high transmission intensity. For each model, parameters governing transmission intensity were scaled to achieve the desired prevalence. In M_F changing the transmission intensity alone was insufficient to achieve the targeted 70% prevalence (compare discussion in

109 Flasche et al [15]). Hence, once the effects of increasing the transmission intensity saturated it was kept
110 constant and the duration of specific and non-specific immunity were subsequently decreased to 6 and 12
111 weeks respectively to achieve the targeted prevalence. As M_B was not age structured we split all
112 compartments into an <5y old and a 5 years and older compartment retaining all original parameters and
113 constant rate of transition between the strata such that the mean time spent in the <5 stratum was 5 years. To
114 minimize the effects of stochasticity M_CL was run 10 times and mean values are presented. Stochastic
115 variability on presented outcomes was too small to visualize in the Figures so it was omitted. The Simpson
116 Index was calculated as a measure of serotype diversity [27].

117 We explored two vaccines with alternative compositions each. Firstly, we compared generic vaccines of
118 increasing valency where serotypes are included in order of their competitiveness. Serotype “1” is the
119 strongest competitor, indicated in all models by the highest prevalence in the pre vaccine era, and “20” the
120 lowest. Note that the serotype names do not correspond to the numbering conventionally used for
121 pneumococcal serotypes. Secondly, to approximate PCV7, PCV10, PCV13 and PCV15 we modelled inclusion of
122 serotypes into the vaccine in respect to their observed paediatric prevalence rank among carriage globally. For
123 example PCV7 targets serotypes 4,6B,9V,14,18C,19F and 23F which are the 18th, 2nd, 6th, 5th, 11th, 1st, 3rd most
124 prevalent serotypes globally; hence the PCV7-like vaccine in this work targets model serotypes 1,2,3,5,6,11 and
125 18 (Table 2) [28]. Serotypes of a lower rank than 20 were not included since the models only consisted of 20
126 serotypes.

127 M_B and M_F assume that both immunity, including vaccine induced immunity act as all-or-nothing while the
128 Cobey and Lipsitch model assumes it is leaky. The models were run to predict 1) the impact of vaccination
129 against each targeted serotype [29] (assuming 100% coverage and 55% efficacy) and 2) the effective coverage
130 needed to achieve elimination of VT carriage. We defined effective coverage as vaccine efficacy times vaccine
131 coverage (N.B. in the two models that assume all-or nothing vaccine protection this is equivalent to the fraction
132 of the population that is protected by vaccination, in the M_CL we assumed 100% population coverage and
133 varying vaccine efficacy), and elimination of VT carriage as a reduction of VT carriers of 95% or more. The
134 impact of vaccination is measured as either the percentage reduction in the number of VT carriers, or
135 alternatively with any serotype, in year 10 after the start of vaccination if compared to the year before
136 vaccination (steady state). We choose to report only the impact after 10 years as for this work we were only
137 interested in potential qualitative differences in predictions in the mid to long term of vaccine introduction.

138

139

140 Results

141 Models differed in the proportion of children among the simulated population. M_B assumed an age
142 distribution based on the Gambia and hence that children younger than 5 years old make up 20% of the total
143 population. In both other models that represent high income countries the corresponding proportion was 5%
144 (Figure 1). Pneumococcal carriage prevalence was almost evenly distributed across serotypes in M_F and
145 dominated by fewer serotypes in M_CL. The Simpsons index in children was 0.871, 0.845, 0.885 in the
146 moderate transmission scenario for M_B, M_CL and M_F and 0.925, 0.862, 0.927 in the high transmission
147 scenario. The models differed how the targeted prevalence in children translated into prevalence in older

148 individuals (Figure 1). Carriage prevalence decreases with age except for M_B which was originally designed to
149 be age independent and hence uses the same parameters for both age groups.

150 In the moderate transmission scenario, the vaccine impact against vaccine type carriage 10 years after the start
151 of vaccination of a vaccine with 55% effective coverage decreased with increasing vaccine valency in all three
152 models (Figure 2). The effect of including more VTs was least visible in M_CL where only inclusion of almost all
153 serotypes (15 or more) reduced the impact on VT carriage to allow VT circulation. The M_B predicted the
154 steepest decrease in vaccine impact on VT prevalence as a result of inclusion of highly and moderately
155 competitive serotypes, however, further inclusion of weakly competitive serotypes which were hardly carried
156 in this scenario did not change the impact of vaccination. Similar dynamics were observed for older individuals
157 and the high transmission scenario, however, M_F predicted a small initial increase in vaccine impact on VT
158 carriage before the impact decreased for higher valencies.

159 The impact of vaccination on all serotype carriage measured 10 years after the start of vaccination with a
160 vaccine with 55% effective coverage generally increased with increasing valency. However, for the high
161 transmission scenario M_CL predicted a negative vaccine impact, i.e. an increase in overall pneumococcal
162 carriage through the inclusion of almost all serotypes into the vaccine formulation and only for valencies of 19
163 and higher predicted a positive impact of vaccination, i.e. a reduction in all serotype carriage prevalence.

164 The PCV7-like and PCV10-like as well as the PCV13-like and PCV15-like vaccines were indistinguishable because
165 the global prevalence rank of the respectively added serotypes were larger than the number of serotypes
166 considered in this analysis and hence omitted. All three models predict that the impact of vaccination against
167 pediatric VT carriage is similar (<5% difference) across the PCV-like formulation (Figure 3). However, changes in
168 vaccine impact on carriage with any serotype were more pronounced but followed the dynamics of the generic
169 vaccine; i.e. inclusion of more serotypes further reduced carriage prevalence, except in M_CL in the high
170 transmission scenario.

171 Consistent with the effect of increasing valency on vaccine impact, increasing the valency of the generic vaccine
172 formulation was predicted to increase the effective coverage needed to eliminate VT carriage in both children
173 and older individuals and in both moderate and high transmission intensity settings (Figure 4). In all three
174 models VT elimination in the general population required less than 10% additional effective coverage to
175 elimination VT carriage among children. In contrast to the other models M_CL predicted that addition of up to
176 half of all serotypes into the generic vaccine formulation would not have a profound effect on the effective
177 coverage needed for elimination of VT carriage but that only inclusion of at least 10 serotypes or 15 serotypes
178 in the moderate and high transmission scenario respectively would. Elimination of pneumococci using a pan-
179 valent vaccine was impossible in M_F and also for the high transmission scenario in M_B.

180 For PCV-like vaccines a similar qualitative behavior to the generic vaccine formulations was predicted. The
181 three models predicted that the effective coverage needed to eliminate VT carriage in the population increases
182 by 12, 2 and 11% respectively for the moderate transmission intensity setting if a PCV13 or 15 – like vaccine
183 was used instead of a PCV7 or 10 – like vaccine. In the high transmission intensity setting elimination of VT
184 carriage for the two modelled vaccine formulations was impossible in M_F, required effective coverage larger
185 than 88% and 97% in M_B and required effective coverage of 34% and 37% in M_CL.

186

187 Discussion

188 Pneumococcal conjugate vaccines have substantially reduced the burden of pneumococcal disease worldwide.
189 However, through replacement with serotypes not targeted by the vaccines a sizeable burden remains and has
190 led to ongoing development of vaccines with higher valency. Using qualitative results across three
191 pneumococcal models that span a variety of assumptions on the acquisition of pneumococcal immunity and
192 serotype competition, we here show that serotype competition from NVTs aids VT elimination. Accordingly, we
193 show that targeting an increasing number of serotypes increases the requirements on vaccine efficacy and/or
194 vaccine coverage to achieve elimination of VT carriage. We predict that the relatively small differences in the
195 number of serotypes targeted by current PCV formulations are unlikely to be substantial enough to lead to
196 measurable differences in the ease of VT elimination but that vaccines that target almost all serotypes may
197 allow continued circulation of the most competitive serotypes even if such vaccine was given at high coverage
198 and the vaccine efficacy against carriage was improved over the efficacy of PCVs.

199 Given the qualitative nature of this comparison we have only assessed the impact of vaccine valency on the
200 potential of elimination of pneumococcal carriage. The implications of the results for the disease impact of a
201 switch from current PCV formulations to a pan valent vaccine are complex. Increasing vaccine valency could
202 lead to a net increase in pneumococcal disease burden if the highly competitive serotypes are controlled only
203 through a vaccine with limited valency and are also highly pathogenic while the types not targeted by the
204 formulation with limited valency rarely cause disease. In this case, the small disease benefit of controlling more
205 serotypes could be outweighed by the increased circulation of the serotypes in the limited-valency vaccine. The
206 expansion of PCV formulations thus far to incorporate additional serotypes responsible for significant amounts
207 of disease has tended to emphasize highly invasive serotypes, thereby minimizing the potential problem we
208 highlight for expansions of the valency of PCVs. A recent study suggests a method for such that would continue
209 this beneficial approach [30].

210 In vaccinated persons, these unintended effects might be fully or partially offset through the additional direct
211 vaccine protection against disease, given that PCV formulations thus far have provided >80% protection against
212 disease, with lower efficacy against carriage [29,31–33]. This implies that unintended effects of increased
213 valency of vaccines might be of greatest concern – and thus most deserving of surveillance – in age groups
214 within a population that have not been vaccinated, such as healthy adults in most countries at present. We
215 emphasize that the model-comparison exercise here was designed to assess general trends in the behaviors of
216 the models, rather than to predict specifically how a higher-valency vaccine would act in a particular
217 population. Setting-specific model parameterization is required to allow quantification of the differential
218 impact of vaccine of varying valency on pneumococcal disease.

219 We show that the observation that serotype competition aids VT elimination and hence that increasing the
220 valency of pneumococcal conjugate vaccine is likely to increase the herd immunity threshold is insensitive to
221 different assumptions of paediatric carriage prevalence and vaccine formulation which we consistently
222 explored across all three models. Most importantly we show that this finding is also insensitive to alternative
223 model assumptions of pneumococcal ecology, the mechanisms of between serotype competition and
224 differences in underlying demographics.

225 We made the simplifying assumption that serotype specific direct vaccine effects are the same across vaccines
226 and targeted serotypes and that they follow those of current PCV formulations; i.e. an approximate 55%
227 efficacy against carriage acquisition of any targeted serotype [29]. However, because of the complexities
228 involved in the conjugation procedure of PCVs it is unlikely that using current techniques PCVs will be able to
229 target more than 20 of the over 90 pneumococcal serotypes [34]. Vaccines that target common proteins rather
230 than specific capsules on the other hand may prevent pneumococcal disease by different mechanisms, e.g.
231 enhanced IL-17A mediated nasopharyngeal clearance rather than prevention of acquisition [35]. While
232 inference of the differential population impact of specific pneumococcal vaccines would require a more precise
233 parameterization including the focus on a specific setting, the qualitative results of this work are likely to
234 similarly apply.

235 In a few instances the models predicted changes to pneumococcal ecology following vaccination that seem
236 counter-intuitive at first. In the high transmission scenario, M_CL predicted that overall pediatric carriage
237 prevalence would stay relatively constant (less than 5% change) for vaccines that included up to 8 of the most
238 competitive serotypes, but then increase by up to 40% if more serotypes were targeted by the vaccine to finally
239 reduce overall carriage by targeting at least 19 serotypes (Figure 2). This is unique to this model because of its
240 inclusion of a gradient in type-specific ability to prevent additional acquisition: carriers of highly-competitive
241 serotypes are more protected against acquisition of further serotypes. By protecting against the most
242 competitive serotypes through vaccination the remaining serotypes are under less pressure from competition
243 to a point where they act almost independently. For vaccines that target between 9 and 18 of all serotypes in
244 the high transmission setting the prevalence of untargeted serotype in the virtual absence of competition then
245 adds up to exceed the overall prevalence before vaccination (Appendix Figure 1). Furthermore, in M_CL the
246 impact of vaccination with low valency vaccines is similar in both transmission settings but higher for moderate
247 to high valency vaccines in high transmission settings than in moderate transmission settings. In contrast, most
248 models including M_B and M_F predict that transmission intensity and the herd immunity threshold are always
249 positively correlated [36]. In M_CL that same effect is evident only for vaccines that target all serotypes. For
250 vaccines that target most but not all pneumococci this model predicts that the relatively weak competitive
251 pressure from NVTs in combination with a substantial increase in overall pneumococcal prevalence in high
252 transmission scenarios helps to control VT circulation better than vaccination in a moderate transmission
253 scenario with less transmissible VTs but also lower NVT carriage prevalence that compete with VTs. M_F
254 predicted that, assuming 55% effective coverage in the high transmission scenario, increasing the valency to up
255 to 15 serotypes leads to a small increase in vaccine impact on VT carriage which is qualitative different from all
256 other models and scenarios presented here. This is a result of comparing the impact of vaccination on a
257 different number of serotypes. In particular, reduction in carriage prevalence of e.g. serotype “1” as a result of
258 vaccination in the high transmission scenario steadily declines with increasing valency in M_F (Figure 2).
259 However, the indirect effect of vaccination against serotypes of lower prevalence is greater and hence
260 comparing the impact of vaccination on all vaccine serotypes includes both the counter-acting trends. Only in
261 the high transmission setting in M_F is a net increase in vaccine effects against VTs predicted for low valency
262 vaccines.

263 While the models agree well on the qualitative relation between vaccine valency and the herd immunity
264 threshold we have observed stark differences in the quantitative results. For example M_CL predicted that
265 much lower effective coverage is required for elimination of VT carriage. Many factors contribute to this

266 observation and some could be addressed by more detailed harmonization of the models to a specific setting.
267 However, two intrinsic model assumptions likely drive this behavior: 1) the strength of vaccine protection and
268 2) the strength of serotype competition. M_CL assumes a relatively strong vaccine protection by reducing
269 susceptibility to VT acquisition permanently after vaccination. M_F assumes vaccine protection, albeit non-
270 leaky, to only hold for 10 years while M_B also assumes lifelong protection from vaccination, although
271 modelled as all-or-nothing and hence even stronger than in M_CL. While the evidence suggest PCVs to be leaky
272 [37] little is known about upcoming pan-valent vaccines. Vaccine protection has been found to remain present
273 5 years after completion after childhood immunization [38] but there is some evidence that protection declines
274 over time albeit with a half-life that exceeds 5 years [29]. Further, M_CL has the weakest serotype competition
275 of the models by assuming leaky protection against heterologous acquisition of additional colonizing strains
276 during carriage with the most competitive serotypes providing stronger protection against new acquisition. In
277 comparison M_B and M_F respectively assume competitive exclusion on acquisition and potential co-infection
278 but only after non-leaky heterologous immunity following acquisition has ended. With the relatively weak
279 competition of serotypes in M_CL a targeted pediatric carriage prevalence is achieved with lower transmission
280 intensity and this in turn will ease elimination of vaccine serotypes in comparison to the other models where
281 transmission is more intense. Recent advances in molecular serotyping methods have shown the pneumococci
282 frequently co-colonise [39,40] and while epidemiological studies suggest that carriage induces both
283 homologous and heterologous protection such protection from a single episode of carriage likely is relatively
284 weak [20,41,42].

285

286 **Conclusion**

287 Using three different modelling approaches for pneumococcal ecology that represent a range of alternative
288 assumptions on pneumococcal immunity and serotype competition we found that NVT competition helps
289 vaccines of limited valencies eliminate VT carriage. This implies that new vaccines that targeted the majority of
290 pneumococcal serotypes will benefit less from NVT competition and are likely to offer less indirect protection
291 than current PCVs. Head to head comparison of current PCVs with high-valency vaccines should not only be on
292 the grounds of non-inferiority of direct effects but should also account for indirect effects, and closely monitor
293 IPD endpoints.

294

295 **Declarations**

296 Ethics approval and consent to participate

297 Not applicable

298 Consent for publication

299 Not applicable

300 Availability of data and material

301 All data generated or analysed during this study are included in this published article and its supplementary
302 information files. The model code is available from the authors on reasonable request.

303 Competing interests

304 ML has received research funding from PATH and Pfizer, and honoraria/consulting fees from Affinivax, Pfizer
305 and Antigen Discovery. GLM, CB and SF declare that they have no competing interests.

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309 Authors' contributions

310 SF and ML conceptualised the study. GLM performed the simulations. SF, ML and CB interpreted the results. SF
311 wrote the manuscript with significant contributions from GLM, ML and CB. All authors have read and approved
312 the final manuscript.

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315

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Tables and Figures

Table 1: Summary of the main features of each model of pneumococcal transmission

	Bottomley et al	Cobey & Lipsitch	Flasche et al
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Model type	Compartmental	Individual based	Individual based
Demographics	Gambia	High income country	High income country
Mixing patterns	Homogeneous	Homogeneous	Age-assortative
Natural immunity as a result of infection	<u>non-specific</u> : transient immunity for the duration of infection <u>anticapsular</u> : chance to develop permanent homologous immunity	<u>non-specific</u> : permanent increase in clearance rate, transient reduction in acquisition rate for the duration of infection <u>anticapsular</u> : permanent reduction in susceptibility to homologous infection	<u>non-specific</u> : transient immunity to heterologous infection <u>anticapsular</u> : additional transient immunity to homologous infection <u>other</u> : exposure independent reduction of susceptibility and carriage duration with age
Vaccine induced immunity	Like anticapsular natural immunity but higher chance for protection	Like anticapsular natural immunity but stronger protection	Like anticapsular natural immunity but longer protection

Table 2: PCV formulations and the ranks of each serotype in terms of its global prevalence according to a review on the global distribution of paediatric pneumococcal carriage

	Serotypes (rank)
PCV7	4 (18), 6B (2), 9V (6), 14 (5), 18C (11), 19F (1), 23F (3)
PCV10	+ 1 (31), 5 (38), 7F (32)
PCV13	+ 3 (9), 6A (4), 19A (7)
PCV15	+ 22F (27), 33F (24)

Fig. 1 Model demographics and serotypes distribution before the introduction of vaccination. Upper panel: The cumulative age distribution of the model populations. Lower panel: a stacked barplot to illustrate the predicted serotype distributions (stacked prevalence of serotype specific carriage episodes scaled to the overall carriage prevalence) in children and the rest of the population in low and high transmission settings.

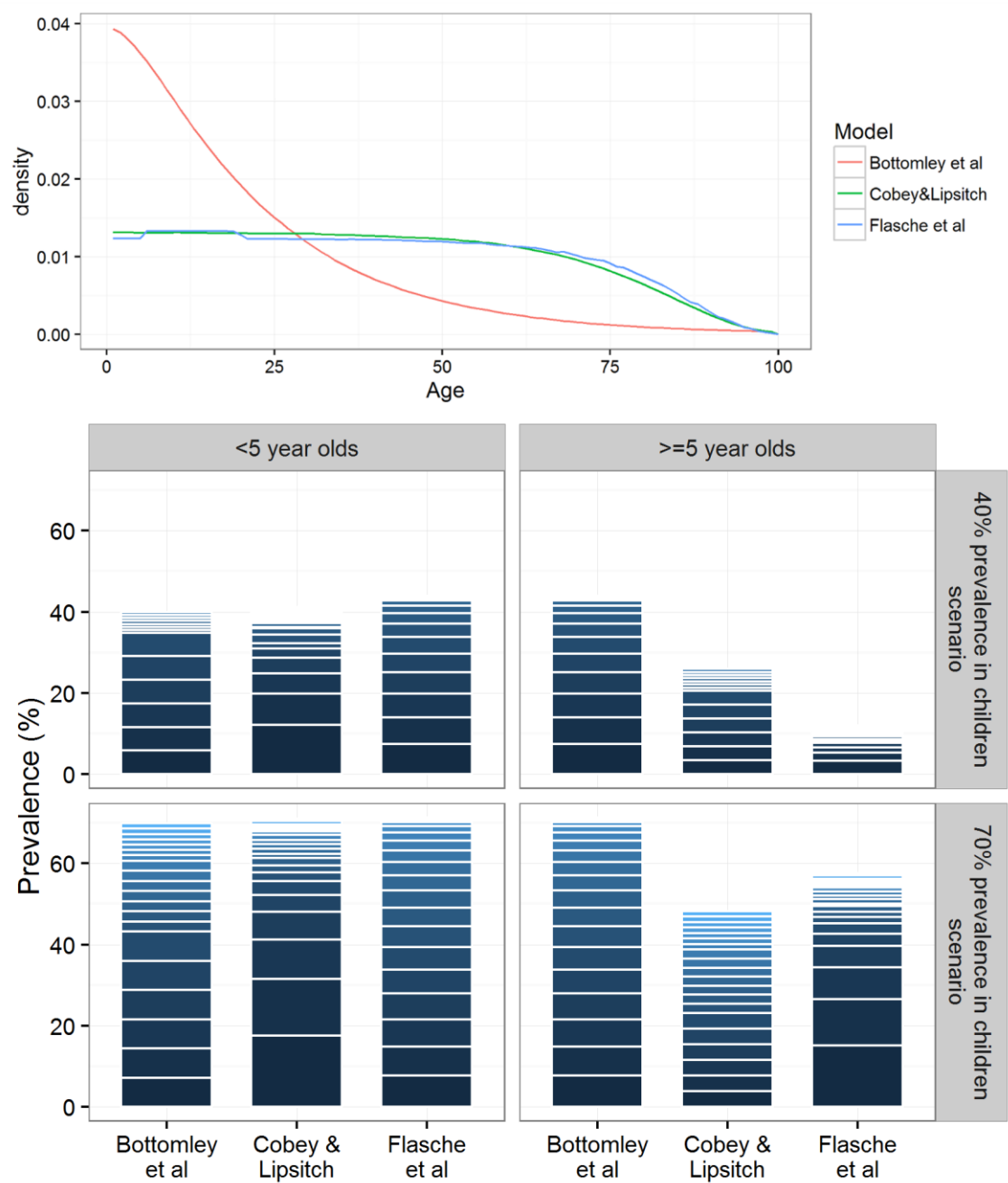
Fig. 2: Predicted percentage reduction in the prevalence of pneumococcal carriage (bottom row), VT carriage (middle row) and carriage of the most competitive serotype (top row) 10 years after vaccine introduction, assuming 55% efficacy against acquisition of pneumococcal VTs and 100% coverage.

Fig. 3: Percentage reduction in the prevalence of pneumococcal carriage 10 years after introduction of a PCV like vaccine, assuming 55% efficacy against acquisition of pneumococcal VTs and 100% coverage.

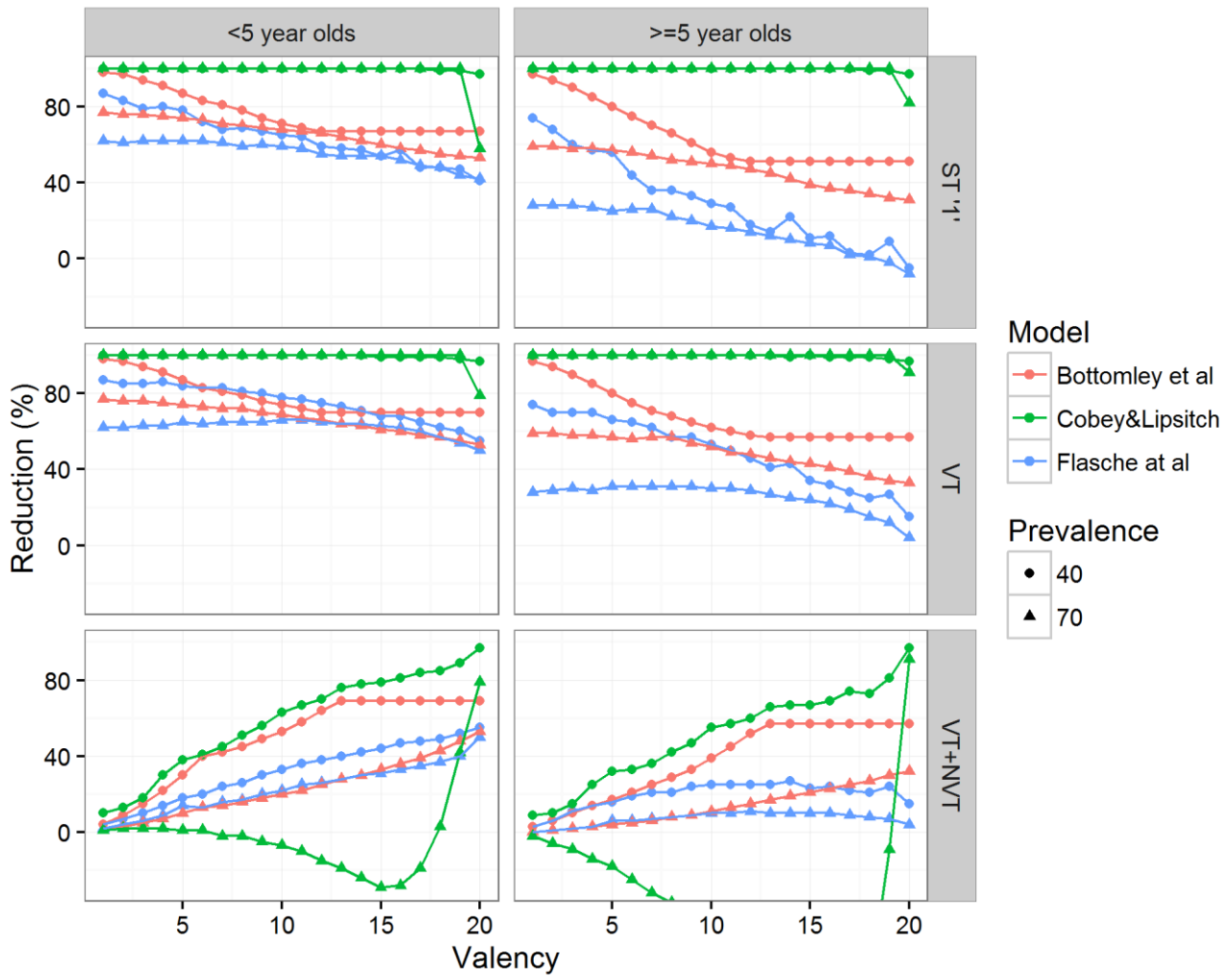
Fig. 4: The effective coverage needed to prevent 95% of VT carriage 10 years after the start of vaccination, assuming serotypes are added to the vaccine in order of their carriage prevalence. At valency 7 and 10 the respective effective coverage for PCV7/10 – like and PCV13/15 – like vaccines are indicated by large dots and triangles in respective colors.

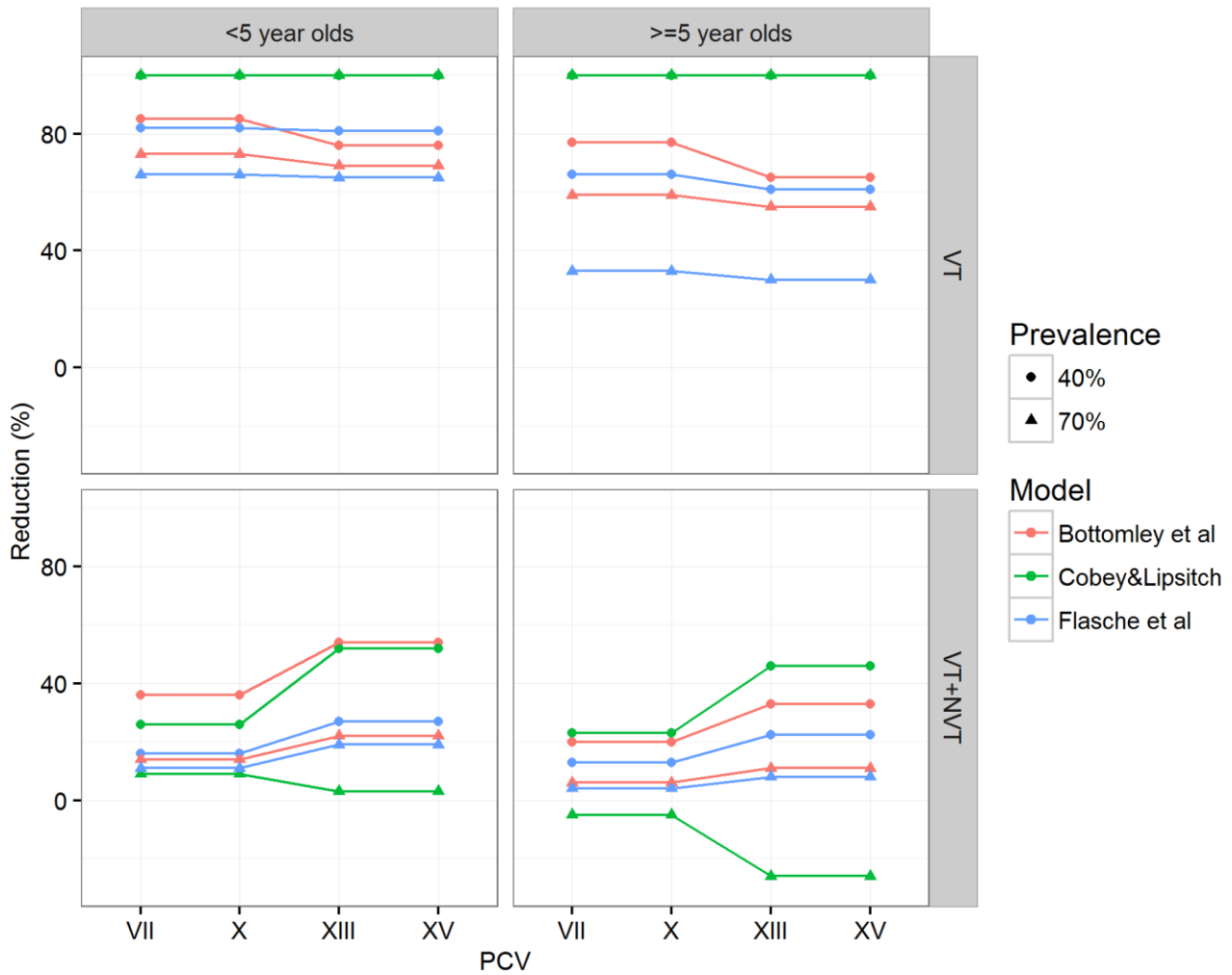
457 Appendix Figure 1: The proportion of carriers that carry 1,2...,6 pneumococci at a time following ten years of
458 vaccination. Rows show different models and columns different transmission intensities indicated by the
459 prevalence of carriage in less than 5-year-old children before vaccination. In M_B each host can only carry one
460 pneumococci at a time and hence the model is not represented here.

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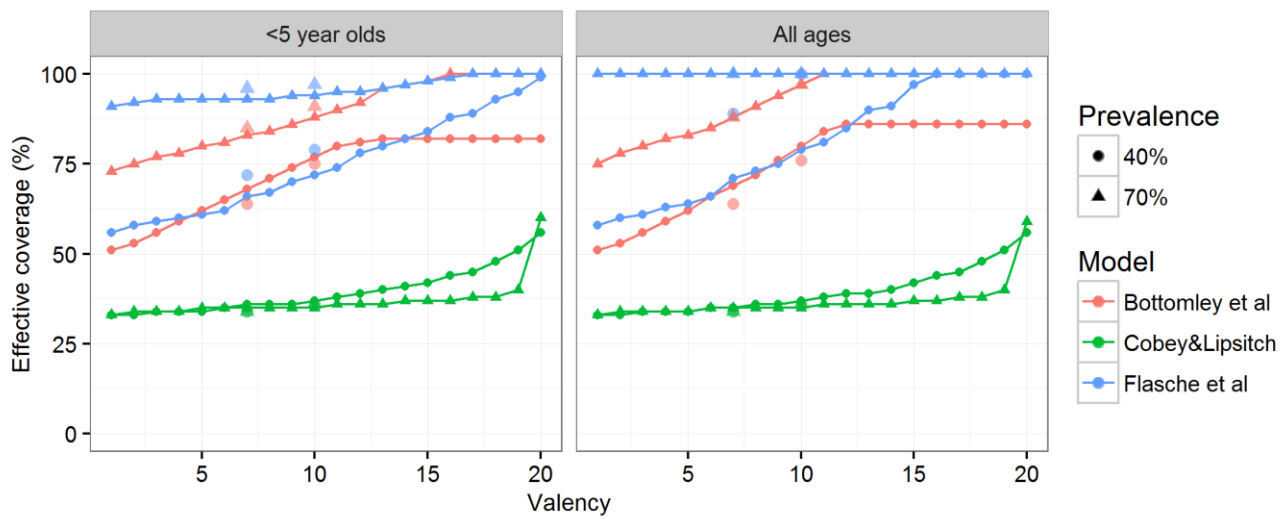


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